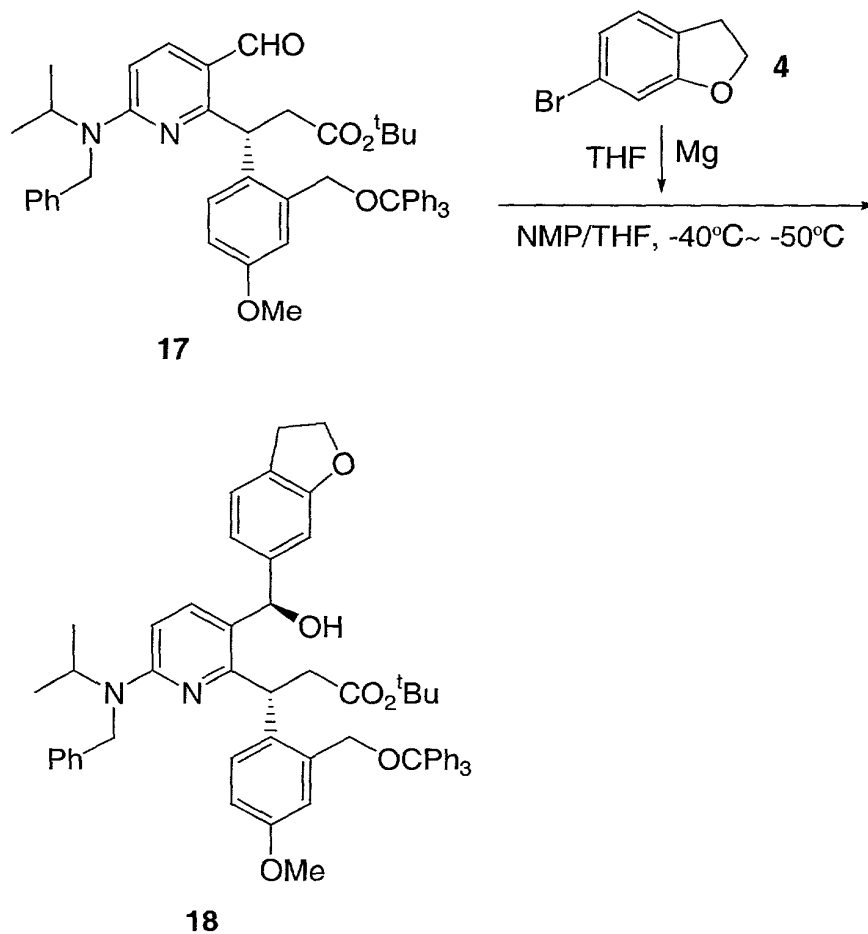


- biphasic mixture is stirred at room temperature for 16 hours. The mixture is then transferred to a separatory funnel and the aqueous layer is removed. The organic layer is washed twice with saturated aqueous NaHCO_3 , and once with water. The organic layer is assayed and concentrated to about 1.3L by removing the solvent in preparation
- 5 for the Florisil treatment. A large sintered glass funnel is packed with a slurry of Florisil (2.58 kg) in 30% MTBE in toluene (2.5L). The toluene solution of **17** is charged to the top of the Florisil plug, and the material is eluted with 30% MTBE in toluene. About 2.4L of solution (containing no product) is collected and discarded. An additional 10L of solution is collected and assayed for **17**. The combined fractions
- 10 containing product are concentrated and azeotropically dried to afford 350.3g of **17** (95% recovery from the florisil treatment). The material is carried forward into the Grignard addition.
- HPLC Conditions: Waters Symmetry C8, 4.6 x 250 mm; TSP UV 2000 dual wavelength, 1 AU/volt output; acetonitrile or (1:1) acetonitrile:water; 1.0mL/min; UV
- 15 detector at 220 nm; 50:50 ACN:water; Retention time at room temperature (min): **9** (19.5), **14** (25.4), **13** (21.4), **16** (40.8) and **17** (27.0).

EXAMPLE 10

Grignard Addition:Step 1: Drying of ArBr (4):

- 5 A solution of ArBr 4 (about 300g, containing 2 to 4w% water) in THF (600mL) is stirred with 60g of molecular sieves overnight. The spent molecular sieves is removed and rinsed with 50mL of THF. Another 60g of fresh molecular sieves is added and the mixture is stirred for about 5 hours (KF of the THF solution is approximately 100µg/mL). The spent molecular sieves is removed and rinsed with
- 10 THF (50mL). Another 30g of fresh molecular sieves is added to the combined THF solution. Upon stirring for about 2 hours, assay of the solution indicates that it contains 322g/L of the compound 4.

Step 2: Grignard Preparation:

To a 2L three-neck round-bottom flask equipped with an efficient condenser, a thermocouple thermometer and a mechanical stirrer is added Mg (27.2g, 1.12mol) and THF (650mL). The ArBr **4** solution in THF (635mL, 322g/L, 204.5g, 1.03mol) is charged into the dropping funnel. The system is degassed by vacuum/N₂ cycle three times and then the mixture is heated to about 50°C. A portion of the ArBr **4** solution (about 50mL) is added and the mixture is stirred until the reaction is initiated. The remaining ArBr solution is added at between 50°C and 60°C for about 2 hours. The mixture is aged at 50°C for about an hour to give a solution of Grignard reagent ArMgBr.

HPLC conditions: Zorbax SB-C8 4.6 x 250 mm; MeCN 40%~90% in 15 min; 1.50mL/min, 10mM Trizma buffer (pH=7); 30°C, UV detection at 220nm; Retention times (min): ArBr **4** (7.4) and ArH (5.3).

Step 3: Grignard Addition:

To a 5L four-neck round-bottom flask equipped with a mechanical stirrer, a thermocouple thermometer and a nitrogen inlet is charged with dry crude conjugate addition product **17** (514g) (assay 258g), NMP (1.25L) and THF (0.75L). The mixture is degassed by vacuum/N₂ cycle three times and then cooled to -50°C. Approximately 1.1L of the Grignard reagent is charged via a cannula in an hour at about -45°C to -50°C. The mixture is aged for an hour at about -50°C. HPLC is used to monitor the completion of the reaction. More ArMgBr may be added if necessary. The reaction is quenched by cannulating the reaction mixture into an aqueous NH₄Cl (1.7L 15w%) with stirring for about 40 minutes. Toluene is added to aid the layer separation. The organic layer is then washed with NH₄Cl (15w%, 0.5L x 2) and brine (1L) and then concentrated to a minimum volume (about 0.8L). It is then dried by flushing with more toluene (final weight after the flush is 744g). HPLC assay indicates the presence of 294g of the product **18** (98% yield) in the residue. The diastereoselectivity is about 96/4.

HPLC conditions: Zorbax SB-C8 4.6 x 250mm; MeCN 60%~95% in 15 min; 1.50mL/min, 10mM Trizma buffer (pH=7); 30°C, UV detection at 220nm; Retention times (min): conjugate addition product **17** (18.0) and Grignard addition product **18** (18.7).